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(54) Title: COMPOSITIONS CONTAINING THIAMPHENICOL AND DICLOFENAC

(57) Abstract

A combination of Thiamphenicol and Diclofenac for use in veterinary medicine in the treatment of infections associated with inflammatory conditions.

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"COMPOSITIONS CONTAINING THIAMPHENICOL AND DICLOFENAC"

The present invention relates to a combination of Thiamphenicol and Diclofenac for use in veterinary medicine in the treatment of infections associated with inflammatory conditions.

Prior art

The various organs and systems affected by infections very frequently suffer from the effects of inflammation itself (swelling, pain, loss of function, increase in mucous or mucous/catarrhal secretions, etc) as well as by a general symptomatology characterized by fever, anorexia, sensory dulling, etc.

In the veterinary field, damages caused by inflammation are sometimes more serious than those due to the infection itself, both in terms of health of the animal and loss of the productions or quality alterations of the products (for example, quality of the milk in case of mastitis).

In veterinary practice, but also in humans, an antibiotic and an antiinflammatory are often administered simultaneously, but in different formulations, to counteract the noxious effects of the infection associated with inflammatory conditions. This kind of treatment involves the unnegligible drawback of repeated administrations, with consequent possible errors in times and dosages of the different products, in addition to the inconvenience for the patient.

In the veterinary field, a combination of Oxytetracycline (antibiotic) with Flunixin meglumine (antiinflammatory) is known. The drawback of this

combination is that it is effective only against a narrow spectrum of infections caused by Gram+ and Gram- bacteria, its use being therefore restricted.

Furthermore, compositions of antibiotic and steroidal antiinflammatories for the topical use are known.

It has surprisingly been found that the combination of Thiamphenicol with Diclofenac in a single formulation is more effective, in the treatment of infections associated with inflammatory conditions, than single administrations of the two active principles.

THIAMPHENICOL is an antibiotic belonging to the class of phenicolates having a wide spectrum antibacterial activity. At the pharmacokinetic/pharmaco-dinamic level, Thiamphenicol has a low plasma protein binding, a rapid and complete absorption, a high tissue distribution; moreover it is not metabolized, therefore it circulates in the free form in the body.

DICLOFENAC is a molecule having higher antiinflammatory, antipyretic and analgesic activities than the other NSADs. At the pharmacokinetic level, Diclofenac is quickly and completely absorbed and largely distributed in tissues.

In addition to the advantage of clinical effectiveness in the treatment of the infections associated with inflammation, the combination of the two compounds in a single formulation provides the following advantages in the veterinary field:

1. reduction of dosage errors;
2. wide-spectrum antibiotic activity, which is particularly useful in veterinary;

3. reduction of the injection sites and of the injected volumes as well as of labour costs;
4. similar absorption and elimination of the two combined compounds, which allows to control the discontinuance times. For the farmer, this means a precise time to slaughter the animal or to milk, and therefore a better control of the operations, mainly in large stock farms.

Disclosure of the invention

The present invention relates to compositions containing Thiamphenicol (TAF) and Diclofenac (DCF) suitable to the oral, parenteral and topical administrations.

The compositions, which can be in the solid, liquid, semisolid or spray form, contain the active principles dispersed or solubilised and make use of pharmaceutically acceptable excipients and carriers, selected to assure a prompt or extended release.

The dosage intervals will range depending on a number of factors, such as the weight of the animal and the seriousness of the infection to treat. Examples of preferred dosages for the various compositions are reported in the following.

Oral unitary dosage compositions: DCF 20 mg - 1g + TAF 100 mg -5 g and preferably DCF 100 mg + TAF 500 mg.

Oral multidose compositions: DCF 0.5 - 5% + TAF 5 - 60% and preferably DCF 5 % + TAF 20%.

Injectable compositions: DCF 2 - 10% + TAF 10 - 50% and preferably DCF 5% + TAF 25%.

Intramammary compositions - ointments/spray: DCF 2 - 10% + TAF 10 - 50% and preferably DCF 5% + TAF 25%.

Topical compositions: DCF 0.5 - 5% + TAF 2 - 10% and preferably DCF 1% + TAF 5%.

Endouterine compositions: DCF 2 - 10% + TAF 10 - 50% and preferably DCF 5% + TAF 25%.

Ophthalmic and auricular compositions: DCF 0.05 - 1% + TAF 0.2 - 5% and preferably DCF 0.1% + TAF 5%.

- The solid compositions (mainly for the oral use) comprise powders, tablets, granulates, capsules (both soft-gelatin and hard-gelatin capsules) pills, lozenges, boluses and pessaries (for the endouterine use).

The antibiotic and the antiinflammatory can be mixed with solid diluents, such as sugars, for example lactose, mannitol, saccharose, sorbitol and/or calcium phosphates; binders, such as starch, gelatin, gums, polyvinylpyrrolidone, cellulose compounds; disintegrants, such as amides and carboxymethylamide, cross-linked polyvinylpyrrolidone, agar, alginic acid and the salts thereof, such as sodium alginate. Furthermore, such compositions can also contain glidants, lubricants and tableting aids such as talc, stearic acid, magnesium stearate, silicic acid, polyethylene glycols, hydrogenated castor oil; pigments, such as titanium dioxide and dyes, release-controlling agents such as cellulose polymers and others.

Anyway, all of the materials used in the pharmaceutical technology can be employed, as far as they are compatible with the active principles.

Alternatively, the active principles can be included in the conventional gelatin capsules in the form of granules, and preferably in the form of suspensions in vegetable or mineral oils, or in low molecular weight

polyethylene glycols. Capsules consist of gelatin and a plasticizer, generally glycerol and sorbitol.

- Syrups, oral suspensions and oral pastes contain the active principles dispersed in a suitable carrier consisting of water, oily solvents, alcohols or polyalcohols and inorganic suspending agents, for example colloidal silicates having a high content in aluminium and magnesium, such as bentonite, veegum, kaolin and colloidal silica, such as Aerosil, Carbosil; organic stabilizers; swelling agents such as alginates, gum arabic, tragacanth, carrageenins, guar gum, agar, and lipophilic thickening agents in case of, for example, oily pastes, synthetic or semi-synthetic agents such as ethylene oxide homopolymers, for example Polyoxil, preferably cellulose ethers, for example methyl- or ethylcellulose, hydroxyethyl cellulose, hydroxypropyl ethylcellulose, carboxymethylcellulose, microcrystalline cellulose; soluble polyvinyl compounds such as polyvinyl acetate, polyvinyl alcohol and polyvinylpyrrolidone; sweetening agents such as glucose, fructose, xylose; dyes; flavours; antioxidants such as sulfites, propylgallates, butyl hydroxyanisol, dithioproponic acid; buffering agents.

The parenteral compositions comprise liquid pharmaceutical forms prepared formulating the antibiotic and the antiinflammatory in a sterile carrier. Active principles can be either suspended or solubilised in the carrier, depending on the nature and concentration thereof. In the preparation of solutions, the active principles are dissolved in mixtures of water and organic solvents, for example N,N-dimethylacetamide, N-

methylpyrrolidone, 2-pyrrolidone, propylene glycol, low molecular weight alcohols, low molecular weight polyethylene glycols, and filtered in sterile before being distributed in suitable containers. Specific adjuvants, such as preservatives, local anaesthetics, buffering agents can be dissolved in the carrier. The composition can be freeze-dried to increase its stability, and commercialized together with a solvent container for reconstitution prior to use.

Parenteral suspensions are prepared substantially the same way, with the exception that the already sterilized active principles are suspended and not solubilised in the carrier. A wetting agent, or a surface-active agent, can be used to facilitate the homogeneous distribution of the active components. Parenteral suspensions are usually oily suspensions with a lipophilic carrier, such as fatty oils, for example sesame oil, fatty acids synthetic esters, such as ethyl oleate, or triglycerids or diglycerids such as fractioned coconut oil and propylene glycol dicapryl dicaprate. In the case of the aqueous suspensions, thickeners such as sodium carboxymethylcellulose, polyvinylpyrrolidone, dextrans, sorbitol and stabilizing agents can be included.

- The preparations for the topical use in the veterinary field are administered through the intramammary, endouterine, ophthalmic and auricular routes and are mainly ointments, creams, gels, salves, and liquid spray products or foams, tinctures and drops. Ointments contain the active principles suitably micronized, dispersed in an emulsified base (cream) or in a single-phase, generally anhydrous excipient. The

oil in water emulsions have a water content > 50%, the water in oil emulsions contain up to 70%, but preferably 20 - 50%, of water or of aqueous phase. Suitable hydrophilic emulsifiers are present, for example non-ionic surfactants, such as fatty acids esters with polyalcohols or ethylene oxide, such as sorbitan polyethoxylates esters (tween), polyoxyethylene alkylethers (cetheareth-20), and ionic derivatives such as alkylsulfonate or arylsulfonate derivatives, such as sodium laurylsulfate, sodium cetylsulfate, and lipohilic emulsifiers such as sorbitan esters, for example sorbitan monooleate and sorbitan isostearate. The oily components of these formulations comprise hydrocarbons, for example white soft paraffin and/or liquid paraffin and/or hard paraffin, natural or synthetic fats, for example coconut oil triglycerid, hydrogenated oils, such as hydrogenated castor oil, glycerol partial esters with fatty acids, such as glyceryl mono- and distearate, fatty acids, for example palmitic and stearic acids, solid waxes, such as beeswax, wool fat, fatty alcohols or esters such as cetyl or stearyl alcohols, or wool wax alcohols derivatives. Excipients for the aqueous phase can be used in creams to prevent drying out, for example polyalcohols such as glycerol, sorbitol, propylene glycol, and/or polyethylene glycol, and also antimicrobial preservatives.

In the case of gels, which can be anhydrous or aqueous, various gelling agents are generally used, such as those already cited for oral suspensions, comprising inorganic compounds, natural, synthetic or semisynthetic organic macromolecules. Endomammary ointments are prepared in

single unit doses, usually tubes-syringes, to facilitate the intracanalicular administration and preserve the sterility of the product.

- Foams and spray solutions are dispensed from pressurized containers containing suitable propellers, for example halogenated hydrocarbons, such as dichlorodifluoromethane and dichlorotetrafluoroethane and hydrocarbons such as butane, propane and isobutane. Such products are obtained preparing a concentrate containing the active principles in the form of a solution, an emulsion or an anhydrous base added with surface-active agents in the case of anhydrous foams. Suitable carriers for topical sprays can be all the organic solvents compatible with the active ingredient and with the characteristics of the container, and in particular, low boiling alcohols, for example ethyl alcohol, low boiling acetals, for example methylal, highly solubilising solvents, such as acetone, N-methylpyrrolidone. Emulsion foams can be similar to the formulations of creams for the topical use, or anhydrous bases in cases of non-aqueous foams mainly containing oils, higher alcohols such as cetylstearyl alcohol, myristyl alcohol, glycols such as propylene glycol, propylene glycol monostearate and generally ethoxylated surfactants, such as vegetable oils polyglycosylated glycerides.

The invention relates to the combination of Diclofenac and Thiamphenicol for the treatment of infections and related inflammatory conditions, preferably in the form of suitable pharmaceutical formulations.

The following examples further illustrate the invention without limiting it.

Example 1

Syrup containing 1% Diclofenac and 2.5% Thiamphenicol

COMPOSITION

diclofenac	1.00 g
thiamphenicol	2.50 g
polyvinylpyrrolidone	2.00 g
polyethylene glycol 200	20.00 g
70% sorbitol solution	25.00 g
veegum	0.50 g
span 20	1.00 g
potassium sorbate	0.10 g
average viscosity sodium carboxymethylcellulose	0.60 g
citric acid	0.20 g
sodium saccharin	0.30 g
water	q.s. to 100.00 ml

Separately prepare a dispersion of the active principles in polyethylene glycol, span 20 and sorbitol. In 30 % of the water volume dissolve in succession citric acid, potassium sorbate, polyvinylpyrrolidone and disperse veegum and carboxymethylcellulose by means of a turbine diffuser. Add the dispersion of the active principles and dilute to final volume with water.

The resulting suspension has pH 4.20 and viscosity of 150 cPs.

Example 2

Antimastitis ointment containing 5% Diclofenac and

20% Thiamphenicol

COMPOSITION

micronized diclofenac	5.00 g
micronized thiamphenicol	20.00 g
white soft paraffin	10.00 g
fatty acids mono and diglycerids	10.00 g
polyoxyethylenated cetylstearyl alcohol	1.00 g
light liquid paraffin	q.s. to 100 ml

Heat the fatty components in a suitable fatty mass melter to a temperature 15°C higher than the melting temperature of the mixture.

Filter the mixture in sterile with a suitable filtering system equipped with a 0.2 µ cartridge previously heated at 90°C and transfer the mixture by means of a pump into a suitable turbodiffuser, cool down to 30°C then incorporate the previously sterilized active principles by suction under vacuum. Keep turbine stirring for 15 - 20', not exceeding a temperature of 50°C. Distribute the resulting ointment in sterile in 5 ml tubes-syringes.

The ointment is whitish and its viscosity is 300.000 cPs.

Example 3

Ophthalmic and auricular drops containing 0.1% sodium Diclofenac and 0.5% Thiamphenicol

COMPOSITION FOR 1 POWDER VIAL

sodium diclofenac	0.01 g
micronized sterile thiamphenicol	0.05 g
boric acid	0.07 g
borax	0.0075 mg
polyvinylpyrrolidone	0.100 g

COMPOSITION FOR 1 SOLVENT VIAL

sodium ethylmercurithiosalicylate	0.001 mg
distilled water	q.s. to 10 ml

In a volume of water corresponding to 2 ml for each vial dissolve boric acid, borax, polyvinylpyrrolidone and sodium Diclofenac, heating slightly. Filter in sterile the resulting solution and add micronized Thiamphenicol dispersing with a turbine. Distribute the suspension in sterile vials and freeze-dry. Separately prepare the diluent solution, solubilising sodium ethyl-mercurithiosalicylate in the amount of water.

Sterilize the thus formulated 10 ml vials in autoclave at 121°C for 15'.

Example 4

Topical spray containing 1% sodium Diclofenac and 5% Thiamphenicol

COMPOSITION FOR 100 G

sodium diclofenac	1 g
thiamphenicol	5 g
methylal	30 g
absolute ethyl alcohol	q.s. to 100 g
N-methylpyrrolidone	25 g
plastoid B	1.4 g
patent Blue	0.1 g

Distribute 120 g of concentrate in pressurized bombs containing 60 g of 25:75 propane/butane propeller. Prepare the solution of concentrate dissolving at room temperature thiamphenicol and sodium Diclofenac in N-methylpyrrolidone. Heat the solution to 70-75°C and dissolve patent Blue, keeping stirring for 15'. Cool down to 25-30°C.

Separately solubilize plastoid B in the alcohol and methylal mixture and add this solution to that containing the active principles.

Distribute the concentrate in bombs, which are pressurized with the propeller.

Example 5

Injectable solution containing 5% sodium Diclofenac and 25% Thiamphenicol

COMPOSITION

sodium diclofenac	5 g
thiamphenicol	25 g
N,N-dimethylacetamide	40 g
propylene glycol	q.s. to 100 ml

The injectable solution is obtained by solubilizing in succession Thiamphenicol and Diclofenac in N,N-dimethylacetamide and subsequently diluting to final volume with propylene glycol. The resulting solution is filtered in sterile through a 0.2 µ filter and distributed in asepsis into the previously sterilised vials.

Example 6

Tablets containing sodium Diclofenac 100 mg and Thiamphenicol 500 mg

COMPOSITION

sodium diclofenac	100 mg
thiamphenicol	500 mg
lactose for direct tableting	350 mg
anhydrous colloidal silica	30 mg
polyvinylpyrrolidone	50 mg
microcrystalline cellulose	350 mg
maize starch	620 mg
purified water	q.b.

All the solid components are first sieved with a 0.5 mm mesh sieve. Separately a mixture of the active principles and lactose is prepared, which is wet and granulated with a polyvinylpyrrolidone aqueous solution, then dried in a forced circulation air oven for 8h at 60°C. The resulting granulate is sieved through a 0.8 mm mesh rocking sieve and then mixed with the other components for 10'. The completed mixture is tableted in 2 g tablets.

CLAIMS

1. Pharmaceutical compositions for the veterinary use containing a combination of Thiamphenicol and Diclofenac.

2. Compositions as claimed in claim 1, for the oral, parenteral or topical administration.

3. Compositions as claimed in claim 2, for the oral administration, in the form of powders, tablets, granulates, capsules, pills, lozenges, syrups, oral suspensions and oral pastes.

4. Compositions as claimed in claim 2, for the parenteral administration, in the form of boluses, injectable solutions and suspensions.

5. Compositions as claimed in claim 2, for the topical, intramammary, endouterine, ophthalmic and auricular administrations, in the form of ointments, creams, gels, salves, liquid spray products or foams, tinctures, drops, pessaries, gels.

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 912 138 A (POZZI FRANCO ET AL) 27 March 1990 see claims -----	1-5

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